WE CLAIM:

1. A method of separating a first ligand from a second ligand in an affinity matrix system, wherein the first ligand associates *in vivo* with the second ligand and wherein the first ligand and the second ligand associate with each other by electrostatic forces, comprising the steps:
   (a) obtaining a sample containing biological complexes that include the first ligand and the second ligand;
   (b) immobilizing the second ligand on an affinity matrix;
   (c) removing unbound substances from the affinity matrix;
   (d) separating the first ligand from the immobilized second ligand, which remains bound to the affinity matrix during the separation, by decreasing the electrostatic forces between the first ligand and the second ligand; and
   (e) optionally, analyzing the separated first ligand.
2. A method of separating a first ligand from a second ligand in an affinity matrix system, wherein the first ligand associates *in vivo* with the second ligand, wherein the first ligand and the second ligand associate with each other by electrostatic forces, and wherein the second ligand is a recombinant fusion protein containing at least one affinity tag, comprising the steps:
   (a) introducing into a cell or organism a recombinant nucleic acid molecule encoding a fusion protein comprising the second ligand fused to at least one affinity tag that can selectively bind to an affinity matrix;
   (b) expressing the fusion protein;
   (c) obtaining a sample containing biological complexes that include the first ligand and the fusion protein;
   (d) immobilizing the fusion protein on the affinity matrix via the affinity tag;
   (e) removing unbound substances from the affinity matrix;

(f) separating the first ligand from the immobilized fusion protein, which remains bound to the affinity matrix during the separation, by decreasing the electrostatic forces between the first ligand and the fusion protein; and

(g) optionally, analyzing the separated first ligand.

3. A method of separating a first ligand from a second ligand in an affinity matrix system, wherein the first ligand associates *in vivo* with the second ligand, wherein the first ligand and the second ligand associate with each other by electrostatic forces, and wherein the second ligand is a recombinant fusion protein containing at least two different affinity tags, comprising the steps:

(a) introducing into a cell or organism a recombinant nucleic acid molecule encoding a fusion protein comprising the second ligand fused to at least two different affinity tags that can selectively bind to different affinity matrixes;

(b) expressing the fusion protein;

(c) obtaining a sample containing biological complexes that include the first ligand and the fusion protein;

(d) immobilizing the fusion protein on a first affinity matrix via a first affinity tag;

(e) removing unbound substances from the first affinity matrix;

(f) separating the fusion protein from the first affinity matrix;

(g) immobilizing the fusion protein on a second affinity matrix via a second affinity tag, which is different than the first affinity tag;

(h) removing unbound substances from the second affinity matrix;

(i) separating the first ligand from the immobilized fusion protein, which remains bound to the second affinity matrix during the separation, by decreasing the electrostatic forces between the first ligand and the fusion protein; and

(j) optionally, analyzing the separated first ligand.

4. A method of separating a first ligand from a second ligand in an affinity matrix system, wherein the first ligand associates *in vivo* with the

second ligand, wherein the first ligand and the second ligand associate with each other by electrostatic forces, and wherein the second ligand is a protein complex containing two or more subunits of which are fused to different affinity tags, comprising the steps:

(a) introducing into a cell or organism recombinant nucleic acids molecules encoding fusion proteins comprising the two or more subunits of which are fused to different affinity tags that can selectively bind to different affinity matrixes;

(b) expressing the fusion proteins;

(c) obtaining a sample containing biological complexes that include the first ligand and the fusion proteins;

(d) immobilizing the fusion proteins on a first affinity matrix via a first affinity tag;

(e) removing unbound substances from the first affinity matrix;

(f) separating the fusion proteins from the first affinity matrix;

(g) immobilizing the fusion proteins on a second affinity matrix via second affinity tag, which is different than the first affinity tag;

(h) removing unbound substances from the second affinity matrix;

(i) separating the first ligand from the immobilized fusion proteins, which remain bound to the second affinity matrix during the separation, by decreasing the electrostatic forces between the first ligand and the fusion proteins; and

(j) optionally, analyzing the separated first ligand.

5. The method according to any one of claims 1, 2, 3 or 4, wherein the second ligand is immobilized selectively on the affinity matrix coated with antibody that binds to the second ligand.

6. The method according to claim 2, wherein at least one affinity tag can bind selectively to the Fc domains of immunoglobulin.

7. The method according to claim 6, wherein the at least one affinity tag contains one or more IgG binding regions of Staphylococcus aureus Protein A or Streptococcal protein G.

8. The method according to claim 2, wherein the at least one affinity tag can be separated selectively from the affinity matrix by treatment with a chemical agent.
9. The method according to claim 8, wherein the at least one affinity tag is selected from the group consisting of GST-tag, SBP-tag, calmodulin binding peptide and maltose binding peptide.
10. The method according to any one of claims 3 or 4, wherein the second ligand is separated from the first affinity matrix by enzymatic cleavage.
11. The method according to claim 10, wherein the enzymatic cleavage is cleavage by TEV protease.
12. The method according to any one of claims 3 or 4, wherein the immobilization in step (d) is performed by binding to a solid support coated with a specific antibody and the removal in step (e) is performed by addition of the same antibody.
13. The method according to any one of claims 3 or 4, wherein the immobilization in step (g) is performed by binding to a solid support coated with a specific antibody.
14. The method according to any one of claims 3 or 4, wherein the first affinity tag can bind selectively to the Fc domains of immunoglobulin.
15. The method according to claim 14, wherein the first tag contains one or more IgG binding regions of Staphylococcus aureus Protein A (SpA-tag) or Streptococcal protein G (SpG-tag).
16. The method according to any one of claims 3 or 4, wherein the first affinity tag can be separated selectively from the first affinity matrix by treatment with a chemical agent.
17. The method according to claim 16, wherein the first affinity tag is from the group consisting of GST-tag, SBP-tag, calmodulin binding peptide and maltose binding peptide.
18. The method according to any one of claims 3 or 4, wherein the second affinity tag can be separated from the first affinity matrix by treatment with a chemical agent.

19. The method according to claim 18, wherein, the second affinity tag is from the group consisting of GST-tag, SBP-tag, calmodulin binding peptide and maltose binding peptide.
20. The method according to any one of claims 3 or 4, wherein the second affinity tag can bind selectively to the Fc domains of immunoglobulin.
21. The method according to claim 20, wherein the second tag contains one or more IgG binding regions of Staphylococcus aureus Protein A (SpA-tag) or Streptococcal protein G (SpG-tag).
22. The method according to any one of claims 1 to 21, wherein the first and second ligand are separated by decreasing the electrostatic forces between the first and second ligand by increasing the ionic strength of the system.
23. The method according to claim 22, wherein the ionic strength of the system is increased with a chemical agent.
24. The method according to claim 23, wherein the chemical agent is KCl.
25. The method according to claim 23, wherein the change of the concentration of the chemical agent is less than 30 mM.
26. The method according to claim 23, wherein the change of the concentration of the chemical agent is between 30 mM and 300 mM.
27. The method according to claim 23, wherein the change of the concentration of the chemical agent is between 300 mM and 700 mM.
28. The method according to claim 23, wherein the change of the concentration of the chemical agent is between 700 mM and 2 M.
29. The method according to any one of claims 1 to 21, wherein the first and second ligand are separated by decreasing the electrostatic forces between the first and second ligand by changing the pH of the system.
30. The method according to any one of claims 1 to 21, wherein the first ligand is separated from the second ligand by enzymatic treatment that modifies the second ligand.
31. The method according to any one of claims 1 to 21, wherein the first ligand is separated from the second ligand by enzymatic treatment that modifies the first ligand.

32. A method of identifying and eliminating contaminant proteins in a cellular lysate sample that contaminant the affinity matrix system comprising preparing a cellular lysate from an organism or cell devoid of an affinity tag, and performing the same purification steps as with a cellular lysate from the same organism or cell containing an affinity tagged ligand.

33. A method of identifying and eliminating contaminant proteins in a cellular lysate sample that contaminant the affinity matrix system comprising comparing the ligands that bind to several biologically unrelated fusion proteins from the cellular lysate and identifying the common one as contaminants.

34. The method according any one of claims 1 to 31, wherein after the separation of the second ligand from the first ligand, the immobilized second ligand is mixed with a cellular lysate from a different or same organism, and after removal of the unbound substances, the first ligand is separated from the second ligand.

35. The method according to claim 34, wherein an affinity tagged second ligand is covalently cross-linked to the affinity matrix after the separation of the second ligand from the first ligand and before the immobilized second ligand is mixed with a cellular lysate from a different or same organism.

36. The method according to any one of claims 1 to 31, wherein a chemical or biomolecule is identified as a drug or pre-drug by its capability to affect selectively the separation of the first ligand from the second ligand when it is added to or removed from the cellular lysate.

37. The method according to claim 36, wherein the second ligand is a protein which contains at least one mutation.

38. The method according to claim 36, wherein the second ligand associates directly or indirectly with a protein that contains at least one mutation.

39. The method according to claims 36, wherein the chemical or biomolecule is designed, synthesized and/or selected for testing by the

capability pf the chemical or biomolecule to bind to the first ligand or second ligand.

40. The method according to any one of claims 36-39, wherein the chemical or biomolecule is designed, synthesized and/or selected for testing by one of the following features: (a) capability of the chemical or biomolecule to bind selectively to the mutated protein; (b) the chemical or biomolecule contains at least one electrostatic charge that is identical to the charge that has been changed as a result of the mutation, and (c) after binding of the chemical or biomolecule to the mutated protein, a electrostatic charge is located at distance between 0 and 0.5 naometers from a mutated amino acid in the mutated protein.

41. The method according to any one of the claims 1 to 40, wherein the second ligand is an enzyme.

42. The method according to any one of the claims 1 to 40, wherein the second ligand is a substrate for an enzyme.

43. The method according to any one of the claims 1 to 40, wherein the second ligand is an enzyme and a substrate for a different enzyme.

44. The method according to claim 43, wherein the second ligand is RNA polymerase or DNA polymerase.

45. A method for identifying protein-protein association as a putative cause for a disease, comprising associating the disease with a mutation that changes the electrostatic properties of a protein by replacing Lysine and/or Arginine and/or Aspartate and/or Glutamate and/or Histidine with an uncharged or oppositely charged amino acid.

46. A method for identifying protein-protein association as a putative cause for a disease, comprising associating the disease with a mutation that changes the electrostatic properties of a protein by replacing an amino acid with Lysine and/or Arginine and/or Aspartate and/or Glutamate and/or Histidine.

47. The method according to any one of claims 1 to 31, wherein protein-protein association as a putative cause for a disease is identified.

48. The method of claim 47, wherein the disease comprises Norrie disease, Alzheimer's disease, Parkinson's disease, beta3-adrenergic receptor gene mutation, achondroplasia, sickle cell anemia, thrombosis, or alpha 1-antitrypsin deficiency.

49. The method according to claims 1-4, wherein the second ligand is a glycoprotein and the affinity matrix is lectin coated beads.

50. The method according to claims 1-4, wherein the second ligand is a nucleic acid, which is part of a nucleoprotein complex and the affinity matrix consists of immobilized nucleic acid with complementary sequence.

51. The method according to claims 1-4, wherein the second ligand is a nucleic acid, which is part of a nucleoprotein complex and is genetically engineered so that it contains a poly-Guanosine and the affinity matrix consists of immobilized poly-dCytosine.

52. A reagent kit comprising at least one chemical agent for separating the first ligand from the second ligand.

53. A reagent kit comprising a buffer for preparation of cellular lysate and washing buffer.